REMARKS

Claims 1-36 and 66-68 have been cancelled. Claims 37-65 are pending. Claims 37-50 and 62-65 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 51, 52, 56, 57 and 61 have been amended and claims 51-59 are currently under examination. Applicants respectfully submit that all amendments are supported by the original disclosure and do not introduce new matter.

Claim Objection

The Examiner has objected to Claim 57 under 37 CFR 1.75 as being a substantial duplicate of claim 52. Claim 57 has now been amended.

Claim Rejection - 35 USC § 112

Applicants appreciate Examiners withdrawal of the previous rejections of claims 51-55 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim Rejection - 35 USC§112; Written description

Applicants appreciate Examiners withdrawal of the previous rejections of claims 51-55 and 57-61 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner contends that claim 56 as amended continues to recite "lipid hydrolyzing proteins or polypeptides", which is a genus of proteins or polypeptides of which Applicant did not have possession at the time the application was filed.

Claim 56 has now been amended to recite "lysosomal acid lipase."

New Matter

The Examiner has rejected claim 56 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner contends that this rejection was necessitated by claim amendments filed on 05/21/2008.

The amended claim 56 contains the limitation "further comprising the administration of exogenously produced lipid hydrolyzing proteins or polypeptides, contained in a pharmaceutically acceptable carrier". Claim 56 has now been amended to require the administration of (i) DNA encoding lysosomal acid lipase.

Claim 56 has now been amended to recite "lysosomal acid lipase."

Enablement

Applicants appreciate Examiners withdrawal of the previous rejections of claims 51-55 and 57-61 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, as the claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Priority

As documented on page 16 of the Final office action mailed on 11/21/2007, this application 10/776,797 filed on 02/11/2004 is a DIV of 09/775,517 02/02/2001 PAT 6,849,257 which claims benefit of 60/180,362 filed 02/04/2000. The Examiner contends that the provisional application 60/180,362 filed on 02/04/2000 disclosed administration of enzyme into cells, a protein therapy. But, the Examiner contends that the application 60/180,362 did not disclose administration of DNA sequences encoding said enzyme and therefore, the priority of instant application can be dated back to 02/02/2001.

However, as discussed earlier, this is incorrect. The instant application is entitled to the priority date of the provisional application (US 60,180,362) filed on February 4, 2000 because the provisional application disclosed endogenous methods of protein delivery.

The provisional application evidences that the inventors were in possession of the claimed invention, entitling the inventors to claim the benefit of this filing date. The Office is referred to page 3, lines 10-15 of provisional application US 60,180,362, wherein the endogenous method of delivery is disclosed. The provisional application states that the

endogenous protein is "produced or manufactured inside the body by some type of device (biologic or other) for delivery to within or to other organs of the body." This encompasses delivery of DNA for production of proteins by cells endogenously. As such, the provisional application provides support for the pending claims, and accordingly, the priority date of the instant application should be the filing date of this provisional, February 4, 2000.

Claim Rejection - 35 USC §102

The Examiner has rejected claims 51, 52, 57, and 60 under 35 U.S.C. 102(b) as being anticipated by Anderson et al. (Anderson et al., Lysosomal acid lipase mutations that determine phenotype in Wolman and cholesterol ester storage disease. *Mol Genet Metab.* 68(3):333-45, 1999) as evidenced by Du et al. (Du et al. Lysosomal acid lipase deficiency: correction of lipid storage by adenovirus-mediated gene transfer in mice. *Hum Gene Ther.* 13(11):1361-72, 2002).

The Examiner contends that Anderson teaches DEAE-dextran mediated transfection of plasmid vectors containing hLAL (human lysosomal acid lipase, also known as cholesterol ester hydrolase/cholesterol esterase) cDNA inserts into COS-1 cells, and the enzymatic activities of wild type hLAL and various mutated hLAL were analyzed (See Material and Methods, page 334, and Figure 6, Anderson et al., 1999).

The Examiner further contends that the limitation of LAL being a secreted protein as recited in claims 52 and 57, is considered as inherent properties of the recited lysosomal acid lipase, pointing to the reference by Du et al., 2002.

Applicants respectfully traverse this rejection in pointing out that the claims, as amended, require the production of the expression of the DNA sequence in mammalian cells to produce biologically active lysosomal acid lipase capable of hydrolyzing lipids; wherein the expression level is in an amount sufficient to produce secretion of the biologically active lysosomal acid lipase from the cells in a therapeutic amount. Support for this amendment may be found at ¶¶ [0002], [0012], and [0014].

Prior to the invention by the current applicants, it was not known or suggested that mammalian cells could be transfected with a vector and expressed at a level to provide for sufficient secretion. The Anderson et al. (1999) reference merely showed that a vector could be produced that would express LAL. It did not disclose or suggest how to make a stable system

capable of expressing LAL at a level to provide for sufficient secretion that would still be therapeutic. It was not until the Du et al. (2002) reference, work performed by the current applicants themselves, that it was shown that such an effective system could be produced.

The Examiner has rejected claims 51, 52 and 57-59 under 35 U.S.C. 102(b) as being anticipated by Du et al. (Du et al., Molecular and enzymatic analyses of lysosomal acid lipase in cholesteryl ester storage disease. *Mol Genet Metab.* 64(2):126-34,1998) as evidenced by Du et al. (Du et al. Lysosomal acid lipase deficiency: correction of lipid storage by adenovirus-mediated gene transfer in mice. *Hum Gene Ther.* 13(11):1361-72, 2002).

The Examiner contends that Du et al. teaches that the coding region of hLAL generated by polymerase chain reaction was cloned in a baculovirus vector pVT-Bac and transfected into Sf9 insect cells, and hLAL expression was monitored in cell lysates and medium by immunoblot analysis and enzyme assays at 72-h post-transfection with pure recombinant virus.

Applicants respectfully traverse this rejection in pointing out that the claims, as amended, require the production of the expression of the the DNA sequence in mammalian cells to produce biologically active lysosomal acid lipase capable of hydrolyzing lipids; wherein the expression level is in an amount sufficient to produce secretion of the biologically active lysosomal acid lipase from the cells in a therapeutic amount.

Prior to the invention by the current applicants, it was not known or suggested that mammalian cells could be transfected with a vector and expressed at a level to provide for sufficient secretion. The Du et al. (1998) reference was work performed by the current applicants themselves and used insect cells. It was not until the Du et al. (2002) reference, again work performed by the current applicants themselves, that it was shown that such an effective system could be produced.

The Examiner has rejected claims 51, 52, 57-59, and 61 under 35 U.S.C. 102(b) as being anticipated by Sheriff et al. (Sheriff et al., Characterization of lysosomal acid lipase by site-directed mutagenesis and heterologous expression. *JBiol Chem.* 270(46):27766-72, 1995) as evidenced by Du et al. (Du et al. Lysosomal acid lipase deficiency: correction of lipid storage by adenovirus-mediated gene transfer in mice. *Hum Gene Ther.* 13(ll):1361-72, 2002).

Sheriff et al. teaches that the coding region of hLAL generated by polymerase chain reaction was cloned in a baculovirus vector, liposomes were used for initial cotransfections into Sf9 insect cells, and hLAL expression was monitored in cell lysates and medium by immunoblot analysis and enzyme assays at 72-h post-transfection with pure recombinant virus.

As mentioned above, prior to the invention by the current applicants, it was not known or suggested that mammalian cells could be transfected with a vector and expressed at a level to provide for sufficient secretion. The Sheriff et al. (1995) reference was work performed by the current applicants themselves using insect cells. It was not until the Du et al. (2002) reference, again work performed by the current applicants themselves, that it was shown that such an effective system could be produced.

As such, applicants hereby respectfully request that the rejects under 102(b) should be withdrawn and the claims allowed.

Claim Rejection - 35 USC § 103

The Examiner has rejected claims 51 and 53-55 under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (Anderson et al., Lysosomal acid lipase mutations that determine phenotype in Wolman and cholesterol ester storage disease. *Mol Genet Metab.* 68(3):333-45, 1999) in view of Bureau et al. (US PGPUB 2002/0012914, publication date 01/31/2002).

Anderson et al. teaches DEAE-dextran mediated transfection of plasmid vectors containing hLAL (human lysosomal acid lipase, also known as cholesterol ester hydrolase/cholesterol esterase) cDNA inserts into COS-1 cells, and the enzymatic activities of wild type hLAL and various mutated hLAL were analyzed (See Material and Methods, page 334, and Figure 6, Anderson et al., 1999).

Anderson et al. does not teach (i) transfected cells are atheromanous plaque cells or cells of liver as recited in claim 53, and (ii) the vector is introduced to the cells in vivo as recited in claim 55.

However, Bureau et al. teaches that lysosomal acid lipase is a gene associated with lysosomal deficiency in liver metabolism (See paragraphs [0009] and [0074]). Bureau et al. specifically teaches (i) transfection of plasmid DNA or viral vector alone or in combination with

agent vectors in a composition comprising pharmaceutical acceptable excipients into liver tissue (See paragraphs [0002], [0009], [0024], and claim 19), and (ii) an improved method for enhancing electro-transferring nucleic acids that encode therapeutic proteins such as enzymes, cytokines, and hormones, that are the protein products into multi-celled eukaryotic organism cells *in vivo* and *in vitro* (See abstract and paragraphs [0001], [0039]-[0045], Example 10, Bureau et al., 2002).

The Examiner contends that it would have been obvious that it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Anderson et al. regarding transfection of vectors containing hLAL into COS-1 cells with the teachings of Bureau et al. regarding improved methods for transferring nucleic acids combined with protein products into multi-celled eukaryotic organism cells, such as liver cells that metabolize lipids involving enzymatic activity of LAL, to arrive at the claimed methods for providing biologically active lysosomal acid lipase in liver cells either *ex vivo* or *in vivo* as recited in claims 53-55 of instant application.

The Examiner has rejected claims 51 and 53-55 under 35 U.S.C. 103(a) as being unpatentable over Sheriff et al. (Sheriff et al., Characterization of lysosomal acid lipase by site-directed mutagenesis and heterologous expression. *JBiol Chem.* 270(46):27766-72, 1995) in view of Bureau et al. (US PGPUB 2002/0012914, publication date 01/31/2002).

Sheriff et al. teaches that the coding region of hLAL generated by polymerase chain reaction was cloned in a baculovirus vector, liposomes were used for initial cotransfections into Sf9 insect cells, and hLAL expression was monitored in cell lysates and medium by immunoblot analysis and enzyme assays at 72-h post-transfection with pure recombinant virus.

Sheriff et al. does not teach (i) transfected cells are atheromanous plaque cells or cells of liver as recited in claim 53, and (ii) the vector is introduced to the cells in vivo as recited in claim 55.

However, Bureau et al. teaches that lysosomal acid lipase is a gene associated with lysosomal deficiency in liver metabolism (See paragraphs [0009] and [0074]). Bureau et al. specifically teaches (i) transfection of plasmid DNA or viral vector alone or in combination with agents vectors in a composition comprising pharmaceutical acceptable excipients into liver

tissue (See paragraphs [0002], [0009], [0024], and claim 19), and (ii) an improved method for enhancing electro-transferring nucleic acids that encode therapeutic proteins such as enzymes, cytokines, and hormones, into multi-celled eukaryotic organism cells *in vivo* and *in vitro* (See abstract and paragraphs [0001], [0039]-[0045], Example 10, Bureau et al, 2002).

The instant invention is entitled to a priority of invention date which is earlier than February 4, 2000 for at least the reasons described above and in the previously filed responses and declaration. As such, the Bureau et al. reference cannot be prior art to the instant invention and the rejections under 103(a) are rendered moot and should be withdrawn. Applicants assert that this does not imply the date of invention was not earlier than the provisional date.

CONCLUSION

In summary, the rejections under 35 USC §112, first and second paragraph, and 35 USC §102(e) have been overcome and should be withdrawn.

It is therefore respectfully submitted that the claims currently pending in the present application are in form for allowance. Accordingly, reconsideration of those claims, as amended herein, is earnestly solicited.

Applicants also make note herein that the absence of additional patentability arguments should not be construed as either a disclaimer of such arguments or an indication that applicants believe that such arguments are not meritorious.

If Examiner has any questions about the above response, Applicants encourage the Examiner to contact their representative, Stephen R. Albainy-Jenei at (513) 651-6839 or salbainyjenei@fbtlaw.com.

The Commissioner for Patents is hereby authorized to charge any deficiency or credit any overpayment of fees to Frost Brown Todd LLC Deposit Account No. 06-2226.

Respectfully submitted,

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By _____

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